

with polymorphisms in TLR7 had an increased risk of seborrhoeic dermatitis which is known to be associated with yeast overgrowth. The lack of association between chosen TLR4, TLR7 or TLR8 polymorphisms and skin cancer in our group requires confirmation in larger studies and also in the nontransplant population.

Department of Dermatology, Beaumont
Hospital, Dublin 9, Ireland

M.E. LAING

P. DICKER*

*Department of Molecular and Cellular Therapeutics,
Royal College of Surgeons of Ireland,
Dublin 2, Ireland

G.M. MURPHY

E-mail: mrylaing@yahoo.co.uk

References

- 1 Agnese DM, Calvano JE, Hahm SJ et al. Human toll-like receptor 4 mutations but not CD14 polymorphisms are associated with an increased risk of Gram-negative infections. *J Infect Dis* 2002; **186**:1522–5.
- 2 Ameiziane N, Beillat T, Verpillat P et al. Association of the toll-like receptor 4 gene Asp299Gly polymorphism with acute coronary events. *Arterioscler Thromb Vasc Biol* 2003; **23**:e61–4.
- 3 Boekholdt SM, Agema WR, Peters RJ et al. Variants of toll-like receptor 4 modify the efficacy of statin therapy and the risk of cardiovascular events. *Circulation* 2003; **107**:2416–21.
- 4 Arnott ID, Ho GT, Nimmo ER, Satsangi J. Toll-like receptor 4 gene in IBD: further evidence for genetic heterogeneity in Europe. *Gut* 2005; **54**:308.
- 5 International HapMap Project. Available at: <http://www.hapmap.org/> (last accessed 2 June 2009).
- 6 Apetoh L, Ghiringhelli F, Tesniere A et al. Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nat Med* 2007; **13**:1050–9.
- 7 Yusuf N. Protective role of toll-like receptor 4 during the initiation stage of cutaneous chemical carcinogenesis. *Cancer Res* 2008; **68**:615–22.
- 8 Ulrich C, Hackethal M, Meyer T et al. Skin infections in organ transplant recipients. *J Dtsch Dermatol Ges* 2008; **2**:98–105.
- 9 Formicone F, Fargnoli MC, Pisani F et al. Cutaneous manifestations in Italian kidney transplant recipients. *Transplant Proc* 2005; **37**:2527–8.
- 10 Güleç AT, Demirbilek M, Seçkin D et al. Superficial fungal infections in 102 renal transplant recipients: a case-control study. *J Am Acad Dermatol* 2003; **49**:187–92.
- 11 Sun J, Wicklund F, Zheng SL et al. Sequence variants in toll-like receptor gene cluster (TLR6–TLR1–TLR10) and prostate cancer risk. *J Natl Cancer Inst* 2005; **97**:525–32.
- 12 Jelavić TB, Barisić M, Hofman ID et al. Microsatellite GT polymorphism in the toll-like receptor 2 is associated with colorectal cancer. *Clin Genet* 2006; **70**:156–60.
- 13 Purdue MP, Lan Q, Wang SS et al. A pooled investigation of toll-like receptor gene variants and risk of non-Hodgkin lymphoma. *Carcinogenesis* 2009; **30**:275–81.
- 14 Hold GL, Rabkin CS, Chow WH et al. A functional polymorphism of toll-like receptor 4 gene increases risk of gastric carcinoma and its precursors. *Gastroenterology* 2007; **132**:905–12.
- 15 Zheng SL, Augustsson-Balter K, Chang B et al. Sequence variants of toll-like receptor 4 are associated with prostate cancer risk: results from the Cancer Prostate in Sweden Study. *Cancer Res* 2004; **64**:2918–22.
- 16 Zhou XX, Jia WH, Shen GP et al. Sequence variants in toll-like receptor 10 are associated with nasopharyngeal carcinoma risk. *Cancer Epidemiol Biomarkers Prev* 2006; **15**:862–6.

Key words: genetic polymorphisms, skin cancer, toll-like receptors

Conflicts of interest: none declared.

Cutaneous reaction to pegfilgrastim presenting as severe generalized skin eruption

DOI: 10.1111/j.1365-2133.2009.09371.x

SIR, We present a previously unreported severe skin hypersensitivity reaction to pegfilgrastim, a long-acting granulocyte colony-stimulating factor (G-CSF) which is increasingly used for prevention of chemotherapy-induced neutropenia.

A 60-year-old woman presented with right-sided lymphadenopathy and was diagnosed as having stage IIIA Hodgkin lymphoma. She received eight cycles of ABVD chemotherapy (adriamycin, bleomycin, vinblastine and dacarbazine), supported with allopurinol, ondansetron, metoclopramide, co-trimoxazole and conventional G-CSF (lenograstim). This achieved complete remission. No skin problems were reported.

Six years later she developed night sweats, pruritus and right-sided abdominal pain. Widespread relapsed Hodgkin lymphoma was confirmed following cervical lymph node biopsy and staging investigation. She was treated with CHLVP chemotherapy (chlorambucil, vinblastine, procarbazine and prednisolone). Supportive medication was the same, except long-acting G-CSF (pegfilgrastim) was preferred.

Within 24 h of pegfilgrastim administration a localized 10-cm wide florid confluent violaceous reaction, with overlying hyperkeratosis, developed. This was not recognized as an adverse drug reaction. A similar but more severe injection-site reaction occurred with the next cycle, and later became widespread (Fig. 1). Mucosal surfaces were spared. The Medicines and Healthcare Products Regulatory Agency was notified. Both chemotherapy and supportive medication were discontinued for 3 weeks while the eruption resolved. A significant 7-day delay occurred with the ensuing chemotherapy cycle. Skin biopsy of the lesion at the injection site on the right thigh was consistent with a lichenoid drug eruption.

Subsequent complete reintroduction of chemotherapy and supportive medication without G-CSF caused no adverse effect during two subsequent chemotherapy cycles. Regrettably, following a short period of complete remission, the patient had a further relapse and following palliative treatment later died.

Pegfilgrastim is a recombinant human G-CSF with equivalent or superior efficacy to conventional G-CSF¹ and prolonged plasma half-life due to polyethylene glycol (PEG) attachment.² Consequently, only a single prophylactic administration is required during each chemotherapy cycle in contrast to

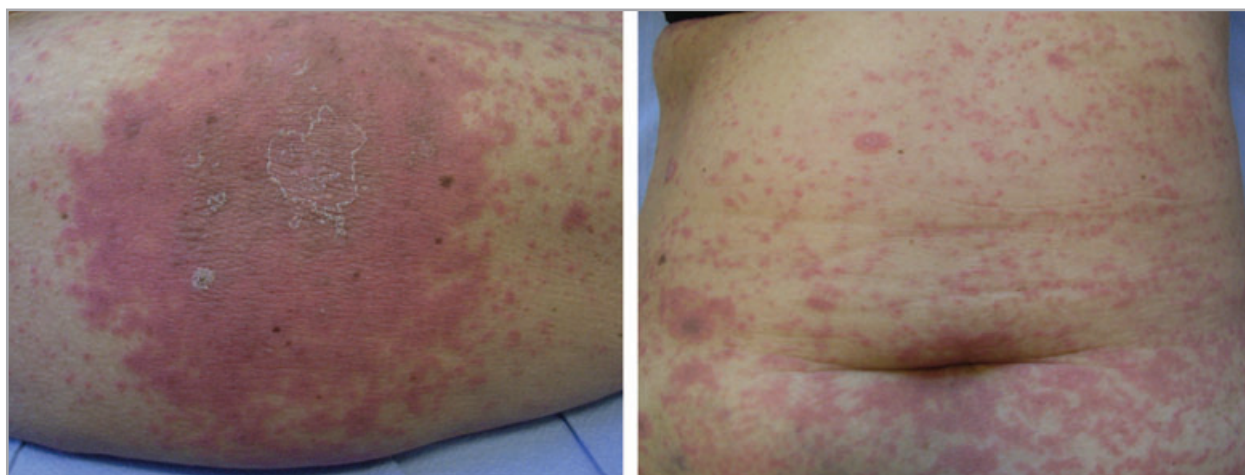


Fig 1. Left: injection site (right thigh), florid local violaceous eruption with overlying hyperkeratosis; right: disseminated discrete lichenoid papules, becoming confluent, over the trunk.

the standard 5–7 day course, improving simplicity and compliance.¹ We highlight a previously unreported and debilitating side-effect to this commonly used drug that necessitated delay in chemotherapy and caused diagnostic difficulties.

There are very few reports of cutaneous reactions to pegfilgrastim during its relatively short period of widespread clinical use. Importantly, cutaneous drug reactions are nonspecific in manifestation, but documented reactions include pyoderma gangrenosum, bullous Sweet syndrome (both attributed to deposition of abnormal neutrophils in the dermis)^{3,4} and a case of type I hypersensitivity with persistent anaphylaxis (due to delayed renal clearance and persistent plasma levels).⁵ To our knowledge, generalized lichenoid eruptions have not been reported before.

A causal role for the G-CSF molecule in our patient is unlikely in the absence of a cutaneous reaction despite ample sensitization to conventional G-CSF during eight cycles of ABVD chemotherapy. Resultantly, modification of G-CSF with PEG is strongly implicated. Cutaneous reactions to PEG are well documented, and include localized immunobullous eruptions,⁶ cutaneous necrosis⁷ and contact dermatitis.⁸ Nevertheless, preparation-specific adverse G-CSF reactions are reported as dose and degree of glycosylation varies,⁹ and therefore cannot be excluded.

Lichenoid reactions at injection sites are common following live attenuated vaccine delivery.¹⁰ The postulated mechanism is a local T-cell-mediated graft-versus-host-like response to vaccine protein sensitization. Lichenoid eruptions have not been reported in other PEG-containing drugs, but it is conceivable that PEG sensitization triggers a comparable reaction directed against keratinocytes.

As the profile and application of pegfilgrastim increase, awareness of potential severe adverse reactions to this drug is important, especially those which, if not recognized early, can result in delay with chemotherapy treatment. We alert clinicians to the possibility of hypersensitivity to pegfilgrastim. In

the presence of a local injection site reaction or any novel coinciding skin condition this drug should be discontinued immediately and replaced by conventional G-CSF preparations if clinically appropriate.

Cancer Centre,
Mount Vernon Hospital,
Northwood, Middlesex HA6 2RN, U.K.
*Department of Dermatology,
Hemel Hempstead General Hospital,
Hemel Hempstead HP2 4AD, U.K.
E-mail: WRSScott@doctors.net.uk

W.R. SCOTT
L. SILBERSTEIN
R. FLATLEY
K.M. ARDESHNA
N. KOROSTOFF*
S. DAWE*

References

- 1 Bhana N. Granulocyte colony-stimulating factors in the management of chemotherapy-induced neutropenia: evidence based review. *Curr Opin Oncol* 2007; **19**:328–35.
- 2 Waladkhani AR. Pegfilgrastim: a recent advance in the prophylaxis of chemotherapy-induced neutropenia. *Eur J Cancer Care (Engl)* 2004; **13**:371–9.
- 3 Miall F, Harman K, Kennedy B, Dyer MJ. Pyoderma gangrenosum complicating pegylated granulocyte colony stimulating factor in Hodgkin lymphoma. *Br J Haematol* 2006; **132**:115–16.
- 4 Draper B, Robbins JB, Stricklin GP. Bullous Sweet's syndrome in congenital neutropenia: association with pegfilgrastim. *J Am Acad Dermatol* 2005; **52**:901–5.
- 5 Hanna GG, Edgar D, Clarke JE. A case of prolonged type 1 hypersensitivity reaction to pegfilgrastim. *Clin Oncol (R Coll Radiol)* 2008; **20**:315–16.
- 6 Gallina K, Brodell RT, Naffah F, Nedorost S. Local blistering reaction complicating subcutaneous injection of pegylated interferon in a patient with hepatitis C. *J Drugs Dermatol* 2003; **2**:63–7.
- 7 Dalmau J, Pimentel CL, Puig L et al. Cutaneous necrosis after injection of polyethylene glycol-modified interferon alfa. *J Am Acad Dermatol* 2005; **53**:62–6.
- 8 Taibjee SM, Prais L, Foulds IS. Allergic contact dermatitis from polyethylene glycol monomethyl ether 350 in Solaraze gel. *Contact Dermatitis* 2003; **49**:170–1.

- 9 White JM, Mufti GJ, Salisbury JR, du Vivier AW. Cutaneous manifestations of granulocyte colony-stimulating factor. *Clin Exp Dermatol* 2006; **31**:206–7.
- 10 Stavrianeas NG, Katoulis AC, Kanelleas A et al. Papulonodular lichenoid and pseudolymphomatous reaction at the injection site of hepatitis B virus vaccination. *Dermatology* 2002; **205**:166–8.

Key words: drug reaction, granulocyte colony-stimulating factor, hypersensitivity, pegfilgrastim, polyethylene glycol

Conflicts of interest: none declared.

Psoriasis: an opportunity to identify cardiovascular risk

DOI: 10.1111/j.1365-2133.2009.09372.x

SIR, In their review of cardiovascular risk factors and their treatment in patients with psoriasis Federman et al.¹ discuss therapeutic interventions which should be considered when dermatologists review patients with psoriasis. We believe that in addition to the 'conventional' risk factors identified in the review certain other cardiovascular risk factors are especially important in patients with psoriasis.

Moderate alcohol consumption has been shown in several epidemiological studies to be cardioprotective; excess alcohol consumption, however, increases cardiovascular risk and mortality.² Poikolainen et al.³ reported excessive alcohol consumption to be the leading cause of excess mortality in patients hospitalized for treatment of psoriasis. Excessive alcohol consumption has been widely documented in patients with psoriasis.^{4,5} Alcohol consumption should therefore be included in any synthesis of cardiovascular risk in patients with psoriasis.

Although mentioned, the authors do not consider homocysteine in formulating a risk profile for patients. Elevated levels of homocysteine have been shown to be an independent risk factor for the development of cardiovascular disease.⁶ The magnitude of the risk is similar to that of smoking and hyperlipidaemia.⁷ In a case-control study, patients had a 7.1 times relative risk greater than controls of having significantly raised levels of homocysteine.⁸ The authors refer to a study by Prodanovich et al.⁹ which found that methotrexate in combination with folate supplementation lowered cardiovascular risk, and hence we contend that homocysteine levels should be measured in patients who have adverse cardiovascular risk profiles. Although intervention does not lower risk it should be assessed.

There is also evidence to support a role for chronic inflammation in psoriasis, as cardiovascular risk factors and inflammatory markers such as fibrinogen have been shown to be raised in patients with psoriasis.¹⁰ Atherothrombotic markers such as fibronectin and platelets may also be raised in psoriasis. Patients with psoriasis also display evidence of hyperinsulinaemia and insulin resistance.¹¹ Insulin levels correlated with disease severity.¹¹ Insulin resistance itself is a risk factor for atherosclerosis. This further endorses the view that patients with psoriasis display a risk factor profile beyond those

conventional risk factors encoded by the Framingham Risk Score such as age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking history and systolic blood pressure.

Treatment of psoriasis may lower cardiovascular risk but certain treatments may adversely affect cardiovascular risk. Ciclosporin may cause hypertension and renal impairment, acitretin may elevate triglycerides and tumour necrosis factor inhibitors may worsen heart failure.

It must also be borne in mind that not all patients with psoriasis have risk factors for cardiovascular disease. It would appear safe to conclude that those with most severe disease have the greatest risk.

We agree with Federman et al. that risk factor evaluation and intervention are very important in psoriasis. We would suggest that additional factors such as excess alcohol consumption, homocysteine levels, markers of inflammation, insulin and the influence of treatment on risk factors be included in a disease-specific assessment of cardiovascular risk in psoriasis.

Department of Dermatology,
St Vincent's University Hospital,
Elm Park, Dublin 4, Ireland
E-mail: tobin.annemarie@gmail.com

A.M. TOBIN
B. KIRBY

References

- 1 Federman DG, Shelling M, Prodanovich S et al. Psoriasis: an opportunity to identify cardiovascular risk. *Br J Dermatol* 2009; **160**:1–7.
- 2 Criqui MH. The role of alcohol in the epidemiology of cardiovascular diseases. *Acta Med Scand Suppl* 1987; **717**:73–85.
- 3 Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital treated patients with psoriasis. *Arch Dermatol* 1999; **135**:1490–3.
- 4 Poikolainen K, Reunala T, Karvonen J et al. Alcohol intake: a risk factor for psoriasis in young and middle aged men? *BMJ* 1990; **300**:780–3.
- 5 Kirby B, Richards HL, Mason DL et al. Alcohol consumption and psychological distress in patients with psoriasis. *Br J Dermatol* 2008; **158**:138–40.
- 6 Graham IM, Daly LE, Refsum HM et al. Plasma homocysteine as a risk factor for vascular disease: the European Concerted Action Project. *JAMA* 1997; **277**:1775–81.
- 7 Wakkee M, Thio HB, Prens EP et al. Unfavourable cardiovascular risk profiles in untreated and treated psoriasis patients. *Atherosclerosis* 2007; **190**:1–9.
- 8 Tobin AM, Hughes R, Hand E et al. Homocysteine status and cardiovascular risk factors in patients with psoriasis: a case control study. *Clin Exp Dermatol* (in press).
- 9 Prodanovich S, Ma F, Taylor JR et al. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005; **52**:262–7.
- 10 Vanizor Kural B, Orem A, Cimsit G et al. Evaluation of the atherogenic tendency of lipids and lipoprotein content and their relationships with oxidant-antioxidant system in patients with psoriasis. *Clin Chim Acta* 2003; **328**:71–82.
- 11 Boehncke S, Thaci D, Beschmann H et al. Psoriasis patients show signs of insulin resistance. *Br J Dermatol* 2007; **157**:1249–51.

Key words: cardiovascular disease, psoriasis

Conflicts of interest: none declared.